OXYBUTYNIN THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefits of provisional application U.S. Serial No. 60/079,429, filed March 26, 1998 under 35 U.S.C. §119(e).

FIELD OF THE INVENTION

This invention pertains to a novel dosage form comprising oxybutynin. The invention relates also to a therapeutic composition comprising oxybutynin, to a therapeutic bilayer comprising oxybutynin, and to a method for administering oxybutynin to a patient in need of oxybutynin.

BACKGROUND OF THE INVENTION

Many people are affected by urinary incontinence. Incontinence is particularly common in the elderly; urinary incontinence is present in approximately fifty percent of nursing home patients, and urinary incontinence is a well known urologic problem in women. It will affect nearly all women in some form during their lifetime, and it is of significant social concern to all humans who experience it.

Urinary incontinence arises from the anatomy and the physiology of the urinary tract, which is composed of a bladder and a sphincter. Anatomically, the bladder consists of the bladder musculature, also known as detrusor, and the trigone. The sphincter includes the bladder neck and the proximal urethra. The detrusor muscle is innervated by the pelvic nerve through the parasympathetic nervous system, and the bladder neck and proximal urethra are innervated by the sympathetic nervous system.

The major functions of the bladder are the storage and expulsion of urine. The bladder is responsible for accommodating increasing volumes of urine at low pressures. Normally, the bladder remains closed during bladder filling and continence is maintained as long as the bladder neck and urethral pressure exceeds intravesical pressure. Voluntary voiding occurs when intravesical pressure exceeds bladder neck and urethral pressure, and involuntary voiding occurs when the intravesical pressure exceeds the bladder neck and urethral pressure.

Involuntary incontinence, also known as urge incontinence, occurs with a loss of a large volume of urine accompanied by symptoms of urgency, frequency and nocturia caused by an unstable bladder or detrusor instability. The patient may lose urine with a change in position or with auditory stimulation. The loss of small volumes of urine usually occurs because of bladder overdistention by a large amount of residual urine referred to as overflow incontinence.

The management of incontinence consists in administering a smooth muscle relaxant, such as oxybutynin, which acts directly on the smooth muscle at the site distal to the cholinergic receptor. The usual dose in the pharmacologic management is repeated doses from two-to-four times a day for oxybutynin. This is difficult to achieve as it requires rigid compliance and it is cost ineffective. Also, oxybutynin is adversely affected by light and it needs protection from air, which properties do not lend the drug to formulation into a dosage form that can administer oxybutynin at a controlled and known rate per unit time to produce the intended therapy.

In light of the above presentation it will be appreciated by those versed in the medical and pharmaceutical dispensing arts to which this invention pertains that a pressing need exists for a dosage form and for a therapeutic composition that can deliver the valuable drug oxybutynin in a controlled, extended dose to a patient in clinical need of incontinence management. The

pressing need exists for an oral dosage form, for a therapeutic composition and for a method of therapy that can deliver oxybutynin at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effect. The need exists further for a dosage form and a therapeutic composition that can deliver oxybutynin protected from light to insure that a complete dose of oxybutynin is administered to the patient and still remains substantially independent of the changing environment of the gastrointestinal tract. The need exists additionally for a dosage form comprising the therapeutic composition that can deliver a therapeutic dose of oxybutynin for its intended effect, for avoiding an overdose, and for lessening the side effects that can accompany the drug. It will be appreciated further by those skilled in the dispensing art that if such a novel and unique dosage form, therapeutic composition and method are made available that can administer oxybutynin in a beneficial dose over time and simultaneously provide oxybutynin while lessening the incidence of both over and under dose, the dosage form, the therapeutic composition, and their accompanying methods would represent an advancement and a valuable contribution to the medical arts.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation it is an immediate object of this invention to provide a dosage form for delivering oxybutynin in a rate-controlled dose, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a dosage form for orally administering oxybutynin in a controlled dose for the nonsurgical treatment of incontinence in a human afflicted with incontinence.

Another object of the invention is to provide a pharmacologic composition comprising oxybutynin indicated for the pharmacologic management of incontinence.

Another object of the present invention is to provide a pharmacologic composition comprising oxybutynin, its racemate, its R-enantiomer and its S-enantiomer, administrable to a human, for lessening the incidence of incontinence.

Another object of the invention is to provide a dosage form comprising a homogenous drug core for dispensing oxybutynin to a human patient.

Another object of this invention is to provide a novel composition that makes available oxybutynin therapeutic activity to a patient in need of oxybutynin therapy.

Another object of the invention is to provide a once-a-day oral sustained release dosage form that delivers a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt at a controlled rate over 24 hours.

Another object of the invention is to provide a dosage form manufactured as an osmotic dosage form that can administer oxybutynin to a biological receptor to produce the desired oxybutynin effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic dosage form that maintains oxybutynin and oxybutynin therapeutically acceptable salts in the dosage form, and thereby provides protection from light until the oxybutynin is released from the dosage form, thereby reducing and/or eliminating the unwanted influences of the gastrointestinal environment of use and still provide controlled administration of oxybutynin over time.

Another objective of the invention is to provide a sustained release dosage form that administers oxybutynin at a sustained release rate accompanied by a lessening of adverse reaction dry mouth.

Another object of the present invention is to provide a dosage form that administers oxybutynin at a controlled rate over time for its therapeutic benefit accompanied by a lessening of possible unwanted side effects.

Another object of the present invention is to provide a dosage form that contains initially crystalline oxybutynin salt protected by a light resistant, semipermeable polymeric wall which oxybutynin can be administered in a controlled dose over time.

Another object of the present invention is to provide a dosage form adapted for the oral administration of α-cyclohexyl-α-hydroxy-benzeneacetic acid 4-(diethylamino)-2-butynyl ester salt in a first composition in contacting, layered arrangement with a second, force-generating composition that operates in combination for the administration of the beneficial ester salt.

Another objective of the invention is to provide a delivery system for a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that achieves an increase in the bioavailability of the drug, reduces the formation of its active metabolites, and achieves a flat drug and metabolite concentration profile as compared to an immediate release dosage administered multiple times a day.

Another object of the present invention is to provide a complete pharmaceutical oxybutynin regimen comprising a composition comprising oxybutynin that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating incontinence by orally administering oxybutynin from a delivery device in a rate-controlled amount per unit time to a warm-blooded animal in need of incontinence therapy.

Another object of the invention is to provide a method for lessening the side-effects accompanying the administration of a member selected from the

group consisting of oxybutynin and its pharmaceutically acceptable salts by administering the drug from a sustained-release dosage form over twenty-four hours.

Another object of the invention is to provide a method of administering oxybutynin to a patient to provide a plasma concentration of oxybutynin.

Another object of the invention is to provide a method for administering oxybutynin from a controlled-release dosage form for lessening the incidence of side effects.

Another object of the invention is to decrease dry-mouth in a patient accompanying the administration of a drug selected from the group consisting of oxybutynin and its pharmaceutically acceptable salts in a sustained-release dose over twenty four hours.

Another object of the invention is to provide a method of administering oxybutynin in a sustained-release profile to lessen side effects.

Other objects, features and advantages of this invention will be more apparent to those versed in the delivery arts from the following detailed specification, taken in conjunction with the accompanying claims.

DRAWING FIGURES OF THE INVENTION

Figures 1 to 6 illustrate the clinical benefits for delivering a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salts, according to the invention.

DETAILED DISCLOSURE OF SPECIFICATION

In one aspect, the present invention provides a therapeutic composition comprising 240 ng to 650 mg (nanogram to milligrams) of oxybutynin or an oxybutynin therapeutically acceptable salt. The oxybutynin

selected from the group consisting of oxybutynin and its pharmaceutically acceptable salts can be present in a dosage form in, for example, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg doses and the like. The pharmaceutically acceptable salt is selected from the group consisting of acetate, bitartrate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, hydrobromide, hydrochloride, lactate, malate, maleate, mandelate, mesylate, methylnitrate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tannate and tartrate. The drug oxybutynin can be present as the racemate, as the R-enantiomer or as the S-enantiomer. The therapeutic composition further contains 20 mg to 250 mg of a hydrogel, such as 20 mg to 250 mg of a polyalkylene oxide of 75,000 to 600,000 weight-average molecular weight. Representative polyalkylenes are a polyethylene oxide of 100,000 weight-average molecular weight or a polyethylene oxide of 200,000 weight-average molecular weight. The therapeutic composition comprises 1 mg to 50 mg of a hydroxypropylalkyl-cellulose of 9,000 to 150,000 average-number molecular weight selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethyl-cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose; 1 mg to 40 mg of an osmotic solute selected from the osmotically effective compounds consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; and 0.01 mg to 5 mg of a lubricant, such as calcium stearate, zinc stearate, magnesium stearate, magnesium oleate, calcium palmitate, sodium suberate, potassium laureate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, and a mixture of salt of fatty, alicyclic or aromatic acid and a fatty, alicyclic or aromatic acid.

The invention provides for the therapeutic composition comprising the oxybutynin to be administered as the composition neat, that is, oxybutynin alone, for increasing the urinary bladder capacity, for diminishing the frequency of uninhibited contractions of the detrusor muscles and its accompanying delay of the desire to void. The invention provides for the therapeutic oxybutynin composition to be surrounded by a wall comprising a semipermeable composition with an exit for delivering the therapeutic composition to a human patient in need of oxybutynin therapy. The invention provides, in an additional embodiment, the therapeutic composition comprising oxybutynin as a therapeutic layer in layered, contacting arrangement with a hydrogel layer that supports the therapeutic layer to yield a bilayered matrix. The hydrogel layer comprises 40 mg to 250 mg of a hydrogel, such as a member selected from the group consisting of 40 mg to 250 mg of a polyalkylene oxide of 1,000,000 to 8,000,000 weight-average molecular weight which are selected from the group consisting of polyethylene oxide and polypropylene oxide; or 40 mg to 250 mg of an alkali carboxymethylcellulose of 10,000 to 6,000,000 weight-average molecular weight such as sodium carboxymethylcellulose or potassium carboxy-methylcellulose; or 0.1 mg to 250 mg of a hydroxyalkylcellulose of 7,500 to 4,500,000 weight-average molecular weight, represented by hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, and hydroxypentylcellulose; 1 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; 0 to 5 mg of a colorant, such as ferric oxide; 0.1 mg to 30 mg of a hydroxypropylalkylcellulose of 9,000 to 225,000 average-number molecular weight, selected from the group consisting of hydroxypropylethylcellulose, hydroxypropylpentylcellulose, hydroxypropylmethylcellulose, and

hydroxypropylbutylcellulose; 0.00 to 1.5 mg of an antioxidant selected from the group consisting of ascorbic acid, butylated hydroxyanisole, butylatedhydroxyquinone, butylhydroxyanisol, hydroxycomarin, butylated hydroxytoluene, cephalm, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propylhydroxybenzoate, trihydroxybutylrophenone, dimethylphenol, diterlbutylphenol, vitamin E, lecithin and ethanolamine; and 0.1 mg to 7 mg of a lubricant selected from the group consisting of calcium stearate, magnesium stearate, zinc stearate, magnesium oleate, calcium palmitate, sodium suberate, potassium laureate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid, and a fatty, alicyclic or aromatic acid.

The invention provides for the therapeutic oxybutynin composition, the therapeutic bilayer comprising the drug oxybutynin layer, and the osmopolymer hydrogel layer to be administered as the composition or the bilayer per se; that is, as the composition or the bilayer together for increasing the urinary bladder capacity, for diminishing the frequency of uninhibited contractions of the detrusor muscles and its accompanying delay of the desire to void. The invention provides additionally for the therapeutic composition and for the compositional bilayer to be surrounded by a wall comprising a semipermeable composition with an exit for delivering the therapeutic composition to a human patient in need of oxybutynin therapy. The invention also provides for a subcoat to surround the therapeutic composition or to surround the bilayer, which subcoat in either embodiment is surrounded by a outer semipermeable wall.

The invention provides a dosage form for the delivery of the therapeutic composition comprising oxybutynin. The dosage form comprises a wall, which wall surrounds an internal lumen or compartment. The wall comprises a semipermeable composition that is permeable to the passage of

fluid and impermeable to the passage of oxybutynin. The wall is nontoxic and it comprises a polymer selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises 75 wt% (weight percent) to 100 wt% of the cellulosic wall-forming polymer; or, the wall can comprise additionally 0.01 wt% to 10 wt% of polyethylene glycol, or 1 wt% to 25 wt% of a cellulose, either selected from the group consisting of hydroxypropylcellulose or hydroxypropylalkylcellulose such as hydroxypropyl-methylcellulose. The total weight percent of all components comprising the wall is equal to 100 wt%. The internal compartment comprises the therapeutic oxybutynin composition in layered position with an expandable hydrogel composition. The expandable hydrogel composition in the compartment increases in dimension by imbibing fluid through the semipermeable wall, causing the hydrogel to imbibe the fluid, expand and occupy space in the compartment, whereby the drug composition is pushed from the dosage form. The therapeutic layer and the expandable layer act together during the operation of the dosage form for the release of oxybutynin to a patient over time. The dosage form comprises a passageway in the wall that connects the exterior of the dosage form with the internal compartment. The dosage form provided by the invention delivers oxybutynin from the dosage form to the patient at a zero order rate of release over a period of 24 hours.

The expression "passageway" as used herein comprises means and methods suitable for the metered release of the therapeutic drug from the compartment of the dosage form. The exit means comprises at least one passageway, including orifice, bore, aperture, pore, porous element, hollow fiber, capillary tube, porous overlay, or porous element that provides for the osmotic controlled release of oxybutynin. The passageway includes a material that erodes or is leached from the wall in a fluid environment of use

to produce at least one dimensioned passageway. Representative materials suitable for forming a passageway, or a multiplicity of passageways comprise a leachable poly(glycolic) acid or poly(lactic) acid polymer in the wall, a gelatinous filament, poly(vinyl alcohol), leachable polysaccharides, salts and oxides. A pore passageway, or more than one pore passageway, can be formed by leaching a leachable compound, such as sorbitol, from the wall. The passageway possesses controlled-release dimensions, such as round, triangular, square and elliptical, for the metered release of oxybutynin from the dosage form. The dosage form can be constructed with one or more passageways in spaced apart relationship on a single surface or on more than one surface of the wall. The expression "fluid environment" denotes an aqueous or biological fluid as in a human patient, including the gastrointestinal tract. Passageways and equipment for forming passageways are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864 and 4,816,263. Passageways formed by leaching are disclosed in U.S. Patent Nos. 4,200,098 and 4,285,987.

DESCRIPTION FOR MANUFACTURING THE COMPOSITION AND DOSAGE FORM OF THE INVENTION

The wall of the dosage form can be formed by using the air suspension procedure. This procedure consists in suspending and tumbling the composition or the layers in a current of air and wall-forming composition until a wall is applied to the oxybutynin forming compartment. The air suspension procedure is well suited for independently forming the wall. The air suspension procedure is described in U.S. Patent No. 2,799,241; J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and ibid. Vol. 49, pp. 82-84 (1960). The wall can be formed with a wall-forming composition in a Wurster®

air suspension coater using an organic solvent, such as acetone-water cosolvent 90:10 (wt:wt) with 2.5 wt% to 7 wt% polymer solids. An Aeromatic® air suspension coater using, for example, a methylene dichloride methanol cosolvent comprising 87:13 (v:v) can be used for applying the wall. Other wall-forming techniques, such as pan coating, can be used for providing the dosage form. In the pan coating system, wall forming compositions are deposited by successive spraying of the composition or the bilayered arrangement, accompanied by tumbling in a rotating pan. A larger volume of cosolvent can be used to reduce the concentration of polymer solids to produce a thinner wall. Finally, the wall of the coated compartments are laser or mechanically drilled, and then dried in a forced air or humidity oven for 1 to 3 days or longer to free the solvent. Generally, the walls formed by these techniques have a thickness of 2 to 20 mils (0.051 to 0.510 mm) with a preferred thickness of 2 to 6 mils (0.051 to 0.150 mm).

The dosage form of the invention is manufactured by standard manufacturing techniques. For example, in one manufacture the beneficial drug oxybutynin and other ingredients comprising a therapeutic composition or comprising the first layer facing the exit means are blended, or they are blended then pressed, into a solid layer. The oxybutynin and other ingredients can be blended with a solvent and formed into a solid or semisolid formed by conventional methods such as ball-milling, calendering, stirring or roll-milling and then pressed into a selected shape. The layer possess dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form. The bilayer possess dimensions corresponding to the internal lumen of the dosage form. Next, the oxybutynin hydrogel layer is placed in contact with the oxybutynin drug layer. The layering of the oxybutynin layer and the hydrogel layer can be fabricated by conventional press-layering techniques. Finally, the two-layer compartment forming members are surrounded and coated with an outer wall. A

passageway is laser drilled or mechanically drilled through the wall to contact the oxybutynin layer, with the dosage form optically oriented automatically by the laser equipment for forming the passageway on the preselected drug surface.

In another manufacture, the dosage form is manufactured by the wet granulation technique. In the wet granulation technique the oxybutynin and the ingredients comprising the first layer are blended using an organic or inorganic solvent, such as isopropyl alcohol-methylene dichloride 80:20 (v:v) as the granulation fluid. Other granulating fluid, such as water, isopropyl alcohol, or denatured alcohol 100% can be used for this purpose. The ingredients forming the first layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the first layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then, the latter prepared wet blend is slowly added to the oxybutynin blend with continual mixing in the blender. The granulating fluid is added until a wet blend mass is produced, which wet mass is then forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 25°C to 40°C. The dry granules are then screened with a 16 mesh screen. Next, a lubricant is passed through an 60 mesh screen and added to the dry screened granule blend. The granulation is put into milling jars and mixed on a jar mill for 2 to 10 minutes. The first and second layer compositions are pressed into a layered tablet, for example, in a Manesty® layer press.

Another manufacturing process that can be used for providing the oxybutynin and hydrogel composition comprises blending their powdered ingredients in a fluid bed granulator. After the powdered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinylpyrrolidone) in a solvent, such as in water, is sprayed onto the respective powders. The coated powders are then dried in a granulator. This

process coats the ingredients present therein while spraying the granulating fluid. After the granules are dried, a lubricant, such as stearic acid or magnesium stearate, is blended as above into the mixture. The granules are then pressed in the manner described above. In another embodiment, when the fluid bed granulating process is used to manufacture the hydrogel layer, the antioxidant present in the polyalkylene oxide can be removed during the processing step. If antioxidant is desired it can be added to the hydrogel formulation; this can be accomplished during the fluid bed granulation described above.

The dosage form of this invention is manufactured in another embodiment by mixing the oxybutynin with composition-forming ingredients and pressing the composition into a solid layer possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to a passageway. In another embodiment, the oxybutynin and other drug composition forming ingredients and a solvent are mixed into a solid, or semi-solid, by conventional methods such as ball-milling, calendering, stirring or roll-milling, and then pressed into a preselected, layer-forming shape.

In the manufactures as presented above, the manufacture comprising a composition or comprising a layer of a composition comprising a hydrogel osmopolymer and an optional osmagent are placed in contact with the layer comprising the drug oxybutynin, and the two layers comprising the layers are surrounded with a semipermeable wall. The layering of the first drug oxybutynin composition and the second hydrogel osmopolymer and optional osmagent composition can be accomplished by using a conventional two-layer tablet press technique. The wall can be applied by molding, spraying or dipping the pressed shapes into wall-forming materials. Another technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layers in a current of air until the wall forming composition surrounds the layers.

Manufacturing procedures are described in Modern Plastics Encyclopedia, Vol. 46, pp. 62-70 (1969); and in Pharmaceutical Sciences, by Remington, 14th Ed., pp. 1626-1648 (1970), published by Mack Publishing Co., Easton, PA. The dosage form can be manufactured by following the teaching in U.S. Patent Nos. 4,327,725; 4,612,008; 4,783,337; 4,863,456; and 4,902,514.

Exemplary solvents suitable for manufacturing the wall, the composition layers and the dosage form include inert inorganic and organic solvents that do not adversely harm the materials, the wall, the layer, the composition and the drug wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethylacetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclo-octane, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES PROVIDED BY THE INVENTION

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become

apparent to those versed in the art in the light of the present disclosure and the accompanying claims.

EXAMPLE 1

A therapeutic oxybutynin composition provided by the invention was prepared as follows: first, 103 grams of oxybutynin hydrochloride was dissolved in 1200 ml (milliliters) of anhydrous ethanol. Separately, 2,280 g of polyethylene oxide of 200,000 weight-average molecular weight, 150 g of hydroxypropylmethylcellulose of 9,200 average-number molecular weight and 450 g of sodium chloride were dry blended in a conventional blender for 10 minutes to yield a homogenous blend. Next, the oxybutynin ethanol solution was added slowly to the blend, with the blender continuously blending until all the ingredients were added to the three component dry blend, with the blending continued for another 8 to 10 minutes. The blended wet composition was passed through a 16 mesh screen and dried overnight at a room temperature of 72°F (22.2°). Then, the dry granules were passed through a 20 mesh screen, 18 g of magnesium stearate was added, and all the ingredients blended again for 5 minutes. The fresh granules are ready for formulation into a therapeutic oxybutynin composition. The therapeutic composition comprises 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% of hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 15 wt% sodium chloride, and 0.6 wt% magnesium stearate. The therapeutic composition can be administered as the composition for its intended oxybutynin therapy.

EXAMPLE 2

An osmopolymer hydrogel composition provided by the invention was prepared as follows: first 1274 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 weight-average molecular weight, 600 g of sodium chloride, and 20 g ferric oxide were separately screened through a 40 mesh screen. Then, all the screened ingredients were mixed with 100 g of hydroxypropylmethylcellulose of 11,200 average-number molecular weight to produce a homogenous blend. Next, 300 ml of denatured anhydrous alcohol was added slowly to the blend with continuous mixing for 5 minutes. Then, 1.6 g of butylated hydroxytoluene was added, followed by more blending, with 5 g of magnesium stearate added with 5 minutes of blending, to yield a homogenous blend. The freshly prepared granulation is passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 63.67 wt% polyethylene oxide of 7,500,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% ferric oxide, 5 mg hydroxypropylmethylcellulose of 11,2000 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 mg magnesium stearate.

EXAMPLE 3

An osmopolymer hydrogel composition provided by the invention was prepared as follows: first 1274 g of pharmaceutically acceptable sodium carboxymethylcellulose comprising a 5,250,000 weight-average molecular weight, 600 g of sodium chloride, and 20 g ferric oxide were separately screened through a 40 mesh screen. Then, all the screened ingredients were mixed with 100 g of hydroxypropylmethylcellulose of 11,200 average-number molecular weight and 100 g of hydroxypropylcellulose of 30,000 average-number molecular weight to produce a homogenous blend. Next, 300 ml of

denatured anhydrous alcohol was added slowly to the blend with continuous mixing for 5 minutes. Then, 1.6 g of butylated hydroxytoluene was added, followed by more blending, with 5 g of magnesium stearate added with 5 minutes of blending, to yield a homogenous blend. The freshly prepared granulation was passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 58.67 wt% the sodium carboxymethylcellulose, 30 wt% sodium chloride, 1 wt% ferric oxide, 5 mg of hydroxypropylmethylcellulose, 5 mg hydroxypropylcellulose, 0.08 wt% butylated hydroxytoluene, and 0.25 mg of magnesium stearate.

EXAMPLE 4

The therapeutic oxybutynin composition and the osmopolymer hydrogel composition were made into a bilayer tablet as follows: first, 147 mg of the oxybutynin composition as prepared in Example 1 was added to a punch die set and tamped. Then, 98 mg of the hydrogel composition as prepared in Example 2 was added and the two layers compressed under a pressure head of 1.0 ton (1000 kg) into a 11/32 inch (0.873 cm) diameter, contacting intimate bilayered tablet. The example was repeated with the hydrogel composition as prepared in Example 3 to produce the tablet comprising two layers.

EXAMPLE 5

The bilayered tablet was manufactured into a sustained-release dosage form that provides a controlled-release of oxybutynin as follows: first, a semipermeable wall-forming composition was prepared comprising 95 wt% cellulose acetate having a 39.8% acetyl content and 5 wt% polyethylene glycol having a number-average molecular weight of 3350 by dissolving the

ingredients in a cosolvent comprising acetone and water in 90:10 wt:wt composition to make a 4% solid solution. The wall-forming composition was sprayed onto and around the bilayered cores as prepared in Examples 2 and 3 to provide a 26.4 mg semipermeable wall.

Next, the semipermeable walled, bilayered tablet was laser drilled to provide a 20 mil (0.51 mm) orifice to contact the oxybutynin layer and the exterior of the dosage form. The residual solvent was removed by drying for 48 hours at 50°C and 50% relative humidity. Next, the dosage forms were dried further for 1 hour at 50°C to remove excess moisture. The dosage form provided by this manufacture provides 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6 wt% magnesium stearate, and 15 wt% sodium chloride in the therapeutic oxybutynin composition. The osmopolymer hydrogel push composition comprises 63.67 wt% polyethylene oxide of 7,500,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% ferric chloride, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 wt% magnesium stearate. The semipermeable wall comprises 95 wt% cellulose acetate comprising 39.8% acetyl content, and 5 wt% polyethylene glycol of 3350 number-average molecular weight. The dosage form comprises an exit passage of 20 mils (0.50 mm) and it has a mean release rate of 0.260 mg/hr for 23.8 hours. The semipermeable wall provides substantial protection from photo (light) degradation of the oxybutynin in the dosage form.

EXAMPLE 6

A dosage form is prepared according to the above examples, comprising a drug layer consisting of 6.67 wt% oxybutynin hydrochloride,

87.83 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5.00 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, and 0.50 wt% magnesium stearate; in layered contact with a push hydrogel layer comprising 58.75 wt% sodium carboxymethylcellulose of 6,000,000 weight-average molecular weight, 30 wt% sodium chloride, 5.00 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 1.00 wt% ferric oxide, 5.00 wt% hydroxypropylcellulose of 75,000 average-number molecular weight and 0.25 wt% magnesium stearate; which bilayered core is surrounded by a semipermeable wall comprising cellulose acetate and polyethylene glycol; and an exit port through the wall for delivering the oxybutynin at a controlled rate over thirty hours.

EXAMPLE 7

The dosage form according to Example 6 wherein the polyethylene oxide has a 300,000 weight-average molecular weight; the hydroxypropylcellulose is a member selected from the group consisting of 25,000, 30,000 or 40,000 average-number molecular weight; and the dosage form comprises 5 mg to 250 mg of oxybutynin pharmaceutically acceptable salt.

EXAMPLE 8

A dosage form was prepared according to the above examples wherein the dosage form of this example comprises a drug oxybutynin layer comprising 5 mg oxybutynin, 111.60 mg polyethylene oxide of 200,000 weight-average molecular weight, 7.35 mg hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.88 mg magnesium stearate, 22.05 mg of sodium chloride, and 0.12 mg of butylated hydroxytoluene; a hydrogel

push layer comprising 62.40 mg of polyethylene oxide of 7,000,000 weight-average molecular weight, 29.40 mg of sodium chloride, 4.90 mg hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 mg of butylated hydroxytoluene, 0.98 mg of red ferric oxide, and 0.24 mg of magnesium stearate; a wall comprising cellulose acetate consisting of a 39.8% acetyl content and polyethylene glycol of 3350 number-average molecular weight in the percentage ratio of 95 wt% cellulose acetate to 5 wt% polyethylene glycol, and an exit passageway in the wall.

EXAMPLE 9

A dosage form was prepared according to the examples provided by this invention wherein the dosage form comprises: a drug oxybutynin layer comprising 5.3 wt% oxybutynin, 82.37 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.25 wt% magnesium stearate, 10 wt% sodium chloride, and 0.08 wt% butylated hydroxytoluene; a push hydrogel layer comprising 63.37 wt% polyethylene oxide of 2,000,000 weight-average molecular weight, 30 wt% sodium chloride, 5 wt% hydroxypropyl-methylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, 1 wt% black ferric oxide and 0.25 wt% magnesium stearate; a wall comprising 99 wt% cellulose acetate comprising a 39.8% acetyl content and 1 wt% polyethylene glycol of 3350 number-average molecular weight; and an exit passageway through the wall for delivering the oxybutynin to a patient.

EXAMPLE 10

An oxybutynin composition was prepared according to the above examples, wherein the composition comprises 10.6 wt% oxybutynin hydrochloride, 79.57 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.25 wt% of magnesium stearate, 7.5 wt% of sodium chloride, and 0.08 wt% butylated hydroxytoluene.

EXAMPLE 11

An oxybutynin composition was prepared according to the above examples wherein the composition comprises 16 wt% oxybutynin hydrochloride, 76.67 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.25 wt% magnesium stearate, 5 wt% sodium chloride and 0.08 wt% butylated hydroxytoluene.

EXAMPLE 12

A hydrogel composition was prepared according to the above examples wherein the composition comprises 58.75 wt% hydroxyethyl-cellulose of 1,300,000 molecular weight, 30 wt% sodium chloride, 10 wt% polyvinylpyrrolidone of 42,000 viscosity-average molecular weight, 1 wt% red ferric oxide, and 0.25 wt% magnesium stearate.

EXAMPLE 13

A dosage form was prepared according to the present invention wherein the dosage form comprises: a drug layer comprising 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6 wt% magnesium stearate, 15 wt% sodium chloride; a push hydrogel layer comprising 58.75 wt% hydroxyethyl-cellulose of 1,300,000 average-number molecular weight, 30 wt% sodium chloride, 10 wt% polyvinylpyrrolidone of 42,000 viscosity-average molecular weight, 1 wt% red ferric oxide, and 0.25 wt% magnesium stearate; a wall comprising 95 wt% cellulose acetate comprising a 39.8% acetyl content, and 5 wt% polyethylene glycol of 3350 number-average molecular weight, an exit orifice of 20 mil (0.50 mm); and a release rate of 0.292 mg per 1 hour for 16.9 hours.

EXAMPLE 14

A dosage form was manufactured according to the present examples wherein the dosage form comprises: a drug oxybutynin layer comprising 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6 wt% of magnesium stearate, and 15 wt% sodium chloride; a push hydrogel layer for pushing the drug oxybutynin layer from the dosage form comprising 63.67 wt% polyethylene oxide of 7,000,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% red ferric oxide, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 wt% magnesium stearate; a subcoat that surrounds the drug oxybutynin layer and

push hydrogel layer wherein the subcoat comprises 95 wt% hydroxyethyl-cellulose, a nonionic water soluble polymer of 90,000 average-number molecular weight; a wall or overcoat comprising 95 wt% cellulose acetate possessing an acetyl content of 39.8% and 5 wt% polyethylene glycol of 3350 number-average molecular weight; a 20 mil (0.50 mm) exit passageway; and an oxybutynin release rate of 0.295 mg per 1 hour over 19.9 hours.

EXAMPLE 15

A sustained-release dosage form manufactured as a tablet designed for oral administration comprising 240 ng to 650 mg of a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salts was made according to the above example, which dosage form provide an essentially flat release profile essentially-free of peaks-and trough plasma oxybutynin concentrations. The dosage form when administered results in a lessening in dry mouth over 24 hours, and the bioavailability of oxybutynin in the lower gastrointestinal tract including the colon.

METHOD OF PRACTICING THE INVENTION

The invention pertains additionally to the use of the therapeutic composition and the dosage form by providing a method for delivering oxybutynin orally to a warm-blooded animal, including a human patient, in need of oxybutynin therapy. The method comprises administering orally the composition to a patient for oxybutynin therapy. The method comprises: (A) admitting orally into the patient a dosage form comprising (B) a semipermeable wall that surrounds (C) a therapeutic composition comprising (A) oxybutynin. The dosage form imbibes fluid through the wall into the dosage form in response to the concentration gradient across the

semipermeable wall. The therapeutic composition in the dosage form develops osmotic energy that causes the therapeutic composition to be administered through the exit (D) from the dosage form over a prolonged period of time up to 24 hours to provide controlled and sustained oxybutynin therapy. The method of the invention comprises also: (A) admitting into the warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of oxybutynin; (2) an oxybutynin drug layer in the compartment comprising oxybutynin; (3) a hydrogel push layer in the compartment comprising an osmotic formulation for imbibing and absorbing fluid for expanding in size for pushing the oxybutynin composition from the delivery device; and (4) at least one passageway in the wall for releasing the oxybutynin; (B) imbibing fluid through the semipermeable wall at a fluid-imbibing rate determined by the permeability of the semipermeable wall and the osmotic pressure across the semipermeable wall causing the push layer to expand; and (C) delivering the therapeutically active oxybutynin from the delivery device through the exit passageway to a warm-blooded animal over a prolonged period of time up to 24 hours. The oxybutynin is administered by the method of the invention in the therapeutic range that avoids a toxic dose and avoids an ineffective dose for antispasmodic therapy. The oxybutynin is administered to patients with uninhibited neurogenic and reflex neurogenic bladder for increased vesual capacity which diminishes the frequency of uninhibited contractions of the detrusor muscle and delays the desire to void. The dosage form is indicated for the relief of symptoms associated with voiding such as urgency, urge incontinence, frequency, nocturia and incontinence in patients in neurogenic bladder.

The drug oxybutynin, identified as OXY, was administered in a clinical study to a number of patients. Oxybutynin is used for treating urinary-

incontinence. Patients administered oxybutynin often quit or discontinue treatment in the prior art due to its anti-cholinergic side effects, which appear to be peak-concentration related. The present invention provides a sustained-release (SR) dosage form that provides a controlled-release (CR) rate of oral administration of oxybutynin designed to provide a continuous plasma drug concentration and avoid peak and valley concentrations. That is, the controlled-extended release dosage form of this invention maintains a therapeutic plasma concentration free of an overdose and free of an ineffective underdose of oxybutynin. In a multiple dose, crossover study, 13 healthy female volunteers of 41 to 68 years of age received either 5 mg of oxybutynin immediate release (IR) every 8 hours, or three 5 mg controlled release (CR) once a day, for four days. The patients blood was sampled on days 1 and 4 to quantify oxybutynin and its desethyl-metabolite (DESOXY) by liquid chromatography mass spectroscopy (LC/MS). The oxybutynin was absorbed rapidly following immediate-release (IR) dosing with mean C_{MAX} of 12 ng/ml. C_{MAX} is the maximum concentration after dosing in the plasma. The drug release kinetics for the controlled-release (CR) plasma concentration rose slowly, reaching a mean peak-concentration C_{MAX} value of 4.2-6.7 ng/ml. The metabolite DESOXY was formed rapidly following immediate release, and its formation paralleled the slow absorption of oxybutynin following controlled release. The DESOXY had a shorter $t_{1/2}$ life compared to OXY, indicating presystemic metabolite formation assuming it to be true metabolite $t_{1/2}$. Single and multiple dose AUC values were similar for both the controlled release and the immediate release suggesting time invariant pharmacokinetics. AUC denotes the area under the plasma concentration profile. The day 4 OXY and DESOXY AUC and their ratios are presented in the Table, where BA denotes the percent bioavailable, that is, BA denotes the relative amount of oxybutynin absorbed from the controlled release (CR)

dosage form compared to the immediate release (IR) dosage form, and C_{MAX} denotes the maximum concentration.

	OXY (AUC) (ng.h/mL)	DESOXY (AUC) (ng.h/mL)	OXY/DESOXY Ratio	OXY (BA%)	DESOXY (BA%)
IR	81	483	0.18		
CR	109	304	0.41	153	69

The higher ratio of OXY-BA following CR compared to IR suggests lower metabolic formation on first pass. This indicates CR could reach the colon within 3-5 hours post dosing. Presystemic cytochrome P450-mediated oxidation may occur in the upper part of the gastrointestinal tract; then, drug released from CR in the colon escapes presystemic metabolism, which could explain the higher OXY/DESOXY ratio and increased OXY BA following CR.

A further clinical study was performed that compared the results from a sustained-release dosage form of the invention with an immediate-release dosage form manufactured as a conventional capsule. The study was a double blind placebo controlled comparison in 82 female urge urinary incontinence patients. In the clinical study, 34 of the female patients were administered the sustained release dosage form of the invention, 32 female patients were administered the immediate release dosage form, and 16 were administered placebo. The dosing program for the sustained release dosage form comprised of 5 mg/day for 2 weeks, then 10 mg/day for two weeks, and finally 15 mg/day for two weeks, administered once a day. The dosing program for the immediate release dosage form comprised of 5 mg/day for 2 weeks, then 10 mg/day for two weeks, and finally 15 mg/day for two weeks, administered in divided doses three times a day. During the study decrease in urge urinary incontinence and anticholinergic side effect observations were made for each dose level.

The mean plasma oxybutynin concentration was maintained flat during a 24 hour period for the sustained release dosage form administered once a day; at steady state (after dosing for 4 days) the mean plasma oxybutynin concentration ranged from 3.2 to 5.5 ng/ml following a 15 mg dose. The plasma oxybutynin concentration following the immediate release administered three times a day showed peak-through fluctuation; at steady state (after dosing for 4 days) the mean peak plasma concentration following 5 mg three times a day was 12.4 ng/ml and the trough concentration was 1.4 ng/ml. The concentrations at other dose levels are proportional to dose.

The clinical study evaluated the number of urge urinary incontinence at each week. The number of urge urinary incontinence episodes was documented by the patients in weekly study-diaries provided to them. The decrease in urge urinary incontinence episodes from baseline was evaluated for the sustained release dosage form and the immediate release dosage form compared to the placebo and were also compared to each other. Efficacy (decrease in urge urinary incontinence) was seen at each dose level for both sustained release dosage form and immediate release dosage form. The dose vs. urge urinary incontinence relationship was analyzed by modeling. The results of the modeling analysis shows a trend towards higher decrease in the urge urinary incontinence episodes for the sustained release dosage form compared to immediate release dosage form. Accompanying Figure 1 depicts the urge-urinary incontinence, U-UI, for patients administered oxybutynin by the sustained release, SR dosage form tablet of the invention, by an immediate release, IR, dosage form and a placebo. The figure depicts the unexpected and striking decrease in urge-urinary incontinence achieved by the invention. Accompanying Figure 2, depicts the decrease in urge-urinary incontinence following administration of oxybutynin by the sustained release dosage form of the invention compared to the immediate release dosage form.

The clinical study considered the anticholinergic side-effect, dry mouth in the patient; dry mouth was classified using a four scale category consisting of no-dry mouth, mild dry mouth, moderate dry mouth, and severe dry mouth. At each weekly clinic visit, patients completed the subjective assessment of anticholinergic effects questionnaire. In addition, the clinic staff telephoned patients at other times during the study to solicit information about anticholinergic effects and other adverse effects. Overall during the study, the side effect dry mouth was reported in fewer patients receiving the sustained release formulation (85% of patients) compared to immediate release formulation (100% of patients). The dose vs. probability of dry mouth relationship was also analyzed by modeling. This modeling analysis shows that the probability of dry mouth is higher for the immediate release dosage form. Accompanying Figure 3 depicts the incidence of dry mouth following treatment by the sustained release, SR, dosage form, the immediate release, IR, dosage form, and a placebo. The drawing figure depicts the dose administered and the degree of dry mouth as none, mild, moderate, and severe.

A therapeutic index was obtained for the clinical study by combining the dose delivered versus the urge urinary incontinence relationship and the dose versus dry mouth relationship. Accompanying Figure 4 is a representation of the therapeutic index comparison between the sustained release, SR, dosage form and the immediate release dosage form, evidencing the decrease in urge-urinary incontinence episodes from the baseline and the probability of dry mouth. In the drawing figure, U-UI denotes urge-urinary incontinence, DM denotes dry mouth, SR denotes sustained release and IR denotes immediate release. The broad-double pointed arrow denotes the unexpected decrease in dry mouth achieved by the sustained release dosage form compared to the very small decrease in dry mouth seen in the narrow-double pointed arrow.

The therapeutic index is defined as the dose or concentration range within which optimum therapy with minimum toxicity i.e. successful therapy is achieved. It can be evaluated as the relative position of the dose vs. efficacy (urge urinary incontinence in this case) and dose vs. toxicity (dry mouth in this case) curve. It is also recognized that a drug with wider therapeutic index is better than a drug with a narrow index.

The results of the clinical study are presented in Figures 1 to 4 and summarized hereafter. Figure 1 shows the urge urinary incontinence in logarithmic scale for all treatments - the line with the star represents a placebo treatment, the line connected by square represents urge urinary incontinence obtained for an immediate release dosage form, and the line connected with dark circles depicts urge urinary incontinence obtained by the sustained release dosage form of the invention. In Figure 1, the expression "U-UI" means urge urinary incontinence, visit day denotes the days the patient visited the clinic and the dose level denotes the mg of oxybutynin delivered by the dosage form on that day, "SR" refers to sustained release dosage form and "IR" refers to immediate release dosage form. As expected and shown in Figure 1, placebo treatment has really no effect on urge urinary incontinence episodes. Whereas following both sustained release and immediate release treatment the number of urge urinary incontinence episodes decrease. Figure 2 depicts the effect produced by the administered drug. In this case higher the decrease better the efficacy. In Figure 2, the solid line which is the decrease in urge urinary incontinence from baseline for the placebo treatment subtracted from the decrease in urge urinary incontinence from baseline for the sustained release dosage form and the dash line which is the decrease in urge urinary incontinence from baseline for the placebo treatment subtracted from decrease in urge urinary incontinence from baseline for the immediate release dosage form. Figure 2 shows the unexpected greater effect in urge urinary incontinence episodes for sustained

release dosage form compared to the immediate release dosage form. Figure 3 depicts the incidence of dry mouth following the administration of placebo, sustained release oxybutynin dosage forms and immediate release oxybutynin dosage forms. In the Figure "SR" refers to sustained release dosage form and "IR" refers to immediate release dosage form, clean area denotes the probability of absence of dry mouth relief, lines slanted left denote the probability of mild dry mouth, crossed lines denotes the probability of severe dry mouth for the administered dose of dry mouth. Figure 4 is a representation of the therapeutic index comparison between the sustained release dosage form and the immediate release oxybutynin dosage form. The therapeutic index is the dose or concentration range within which optimum therapy with minimum toxicity i.e. successful therapy is achieved. It can be evaluated as the relative position of the dose vs. efficacy (urge urinary incontinence in this case) and dose vs. toxicity (dry mouth in this case) curve. Both the dose vs. urge urinary incontinence curve and the dose vs. dry mouth curve is presented in Figure 4. The broad continuous dark line presents the dose vs. urge urinary incontinence relationship for sustained release dosage form and the narrow continuous line presents the dose vs. urge urinary incontinence relationship for immediate release dosage form; the broken dark line represents the occurrence of dry mouth for the sustained release dosage form and the broken narrow line represents the occurrence of dry mouth for the immediate release dosage form. The heavy longer dark double pointed arrow depicts the unexpected greater separation for the dose vs. urge urinary incontinence curve and the dose vs. dry mouth curve for the sustained release dosage form compared to the small double pointed arrow for the immediate release dosage form. This teaches that the therapeutic index is wider for the sustained release dosage form as compared to immediate release dosage form.

The once-daily delivery system provided by this invention maintains an essentially flat concentration throughout the dosing duration of 24 hours, as seen by the absence of peak-to-trough fluctuation, whereas peak-to-trough fluctuation are seen with the multiple daily administration of the immediate release dosage form, as depicted in accompanying Figure 5.

Figure 5 depicts the mean plasma oxybutynin concentration, in ng/mL, steady state on day 4, for an immediate release, IR, dosage form and a sustained release, SR, dosage form.

The delivery system provided by this invention maintains its chemical and physical integrity in a gastrointestinal environment and generally reaches the colo within 3 to 5 hours after oral administration. For some drugs, metabolic activity is higher in the duodendum and jejunum and decreases in the ileum and colon and for some drugs other anti-transport are more prevalent in the colon. The physiological disposition of a drug and its metabolites can depend on the gastrointestinal site of absorption. The clinical studies made available by this invention demonstrated unexpectedly a decrease in oxybutynin metabolism when administered by the sustained release dosage form of the invention. Following the administration of oxybutynin chloride according to the mode and manner of the invention, the relative bioavailability is higher for the drug, combined R+S (racemic) oxybutynin (153%) and also for the individual R- and S- enantiomers of oxybutynin (156% and 187%, respectively) compared to immediate release dosage form (base of 100%); the relative bioavailability is lower for the metabolite, combined R+S (racemic) desethyloxybutynin (69%) and also for the individual R- and S- enantiomers of desethyloxybutynin (73% and 92%, respectively) compared to immediate release dosage form (base of 100%). The relative bioavailability is defined as the following ratio, wherein the Relative Bioavailability for SR = [Total AUC_{inf}(SR) +Dose(SR)] / [Total AUC_{inf}(IR) +Dose(IR)] where AUC_{inf}(SR) is the area under the plasma

concentration curve for the sustained release dosage form and AUC_{inf}(IR) is the area under the plasm concentration curve for the immediate release dosage form. The plasma concentration curves are shown in Figure 5 for both sustained release dosage form and the immediate release dosage form. The ratio, (drug AUC_{inf} / metabolite AUC_{inf}) for the sustained release dosage form was more than twice that for the immediate release. It has been hypothesized that oxybutynin metabolites may be responsible for the side effects (Massad et, J Urol 1992;148:595-597), however, both drug and the metabolite desethyoxybutynin have been shown to have similar potency (Waldeck et al, J Urol 1997;157:1093-1097). The clinical study demonstrated further for an immediate release oxybutynin system, following repeated dosing within a day, the peak drug concentrations are lower in the evening as compared to morning drug administration. This suggests that with a zero-order release rate from a sustained release dosage form, the plasma concentration would go down towards the end of the day. However for the dosage forms provided by this invention delivering oxybutynin hydrochloride it is not the case. On the contrary, with the dosage forms provided by this invention, the plasma concentrations in an essentially steady-state are maintained throughout the day ranging from 3.2 to 5.5 ng/mL following a 15 mg dose. Additionally, the plasma concentration for the sustained release dosage form of the invention administered in the fasting state is similar to that observed when taken after a meal as seen in drawing Figure 6. Drawing Figure 6 illustrates the mean observed plasma R-oxybutynin concentration following the sustained delivery of oxybutynin hydrochloride by the dosage form tablet of the invention 1 X 10 mg qd, wherein qd denotes once-a-day dose, in the fed and fasting states with 43 patients. The data shows food does not affect the manner in which the drug is absorbed from the sustained release dosage form of the invention. Whereas, another delivery product for oxybutynin reported by (Lukkari et al, Eur J Pharmacol, 1996; 50-221-223:

Lukkari et al, 1997; 81:31-34; Nilsson et al, Neurol Urodyn,1997;16:533-542) has properties very different from the sustained release dosage form of this invention. The prior art product is a matrix tablet from which the drug is released by a first order process with about 50% released in 4 hours. The relative oxybutynin bioavailability for the product is similar (approximately 103%) to that of the immediate release product (base 100%) and the relative bioavailability of the metabolite desethyloxybutynin is lower (approximately 68%) as compared to immediate release product (base 100%). The ratio, (drug AUC / metabolite AUC) for the product was only slightly higher (0.13) as compared to IR oxybutynin (0.09). Additionally, when the prior art product is taken after meals the peak oxybutynin (6.2 ng/mL) and desethyoxybutynin concentration (75.5 ng/mL) are two times higher as compared to the fasting state (2.8 ng/mL and 39.5 ng/mL, for oxybutynin and desethyloxybutynin respectively). That is, the prior art delivery product loses the sustained release property when taken with meals.

The sustained release dosage form of the invention was further evaluated in safety and efficacy studies and compared to immediate release. The data from this study was modeled and a dose vs. therapeutic effect (urge urinary incontinence) relationship and a dose vs. side effect (dry mouth) relationship was established. The results of the urge urinary incontinence modeling analysis shows a trend towards higher decrease in the urge urinary incontinence episodes for the sustained release dosage form compared to immediate release dosage form. The dry mouth modeling analysis shows that the probability of dry mouth is higher for the immediate release as compared to the sustained release dosage form of this invention. A therapeutic index was obtained for the clinical study by combining the dose versus the urge urinary incontinence relationship and the dose versus dry mouth relationship. The therapeutic index is defined as the dose or concentration range within which optimum therapy with minimum toxicity i.e.

successful therapy is achieved. It can be evaluated as the relative position of the dose vs. efficacy (urge urinary incontinence in this case) and dose vs. toxicity (dry mouth in this case) curve. The sustained release dosage form of this invention was shown to have an increased therapeutic index (wider separation between the dose vs. urge urinary incontinence curve and dose vs. dry mouth curve) as compared to the immediate release dosage form, as seen in Figure 4. In two additional clinical trials, a SR was administered in doses up to and comprising 30 mg/day which was efficacious in reducing urge urinary incontinence and was well-tolerated with respect to anticholinergic side-effects and especially dry mouth.

In conclusion, the sustained release dosage form of this invention, the oxybutynin plasma concentrations are maintained constant avoiding the rapid rise and peak concentration seen with immediate release oxybutynin, the metabolism of the drug is reduced giving rise to higher oxybutynin bioavailability compared to immediate release oxybutynin and the sustained plasma concentrations are not affected by meals taken with the drug. Finally, the sustained release dosage form of this invention has an increased therapeutic index as compared to immediate release oxybutynin.

The dosage form and the oxybutynin composition of this invention, as seen from the above disclosure, can be used in a method for administering a drug by the oral route, and, in another method, the dosage form and composition can be sized and shaped for administering a drug by the sublingual and buccal routes. The sublingual and buccal routes can be used for quicker therapy, and they can be used when a smaller dose of drug is needed for immediate therapy. The latter routes can be used as a by-pass of the first pass of hepatic metabolism of the drug.

In summary, it will be appreciated that the present invention contributes to the art an unobvious dosage form that possesses practical utility, can administer a drug at a dose-metered release rate per unit time.

While the invention has been described and pointed out in detail with reference to operative embodiments thereof, it will be understood by those skilled in the art that various changes, modifications, substitutions and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the application.